VOL. VII, No. 10 DECEMBER, 1946

BORDEN'S REVIEW

of

NUTRITION RESEARCH

VITAMIN DEFICIENCY IN NERVOUS AND MENTAL DISEASE

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Reviews and summaries of research information concerning nutrition and foods. Published monthly, except July and August, by THE BORDEN COMPANY; officers of the Company: Theodore G. Montague, president; E. L. Noetzel, treasurer; T. D. Waibel, secretary. Editorial office: 350 Madison Avenue, New York 17, N. Y.

VITAMIN DEFICIENCY IN NERVOUS AND MENTAL DISEASE

By **RUTH WOODS**

I. Experimental Findings:

In an early Italian treatise dating back several centuries (1), there appeared the following poignant description of the disease, pellagra:

> "If you should traverse the hills of Brianza and Canavese, you would most likely meet some pitiable wrecks of humanity, with eyes fixed and glassy, with pale and sallow faces and arms fissured and scarred as by a burn or large wound. You would see them advancing with trembling head and staggering gait like persons intoxicated or indeed, as though impelled by an invisible force, now falling on one side, now getting up and running in a straight line like a dog after its quarry and now again falling and uttering a senseless laugh or sob which pierces the heart — such are the pellagrins . . ."

So, although the mental aberrations characteristic of this disease were apparent to the earliest observers of pellagra, it was not until centuries later that faulty diet was implicated as the cause. The dramatic resurrection of the lost minds of violently insane pellagrins through the simple expedient of nourishing foods and synthetic vitamins represents not only an outstanding triumph of nutrition, but also a fundamental contribution of nutrition to psychiatry.

As Sebrell (2) has remarked:

> "Here for the first time is a major psychosis for which we have a specific therapeutic agent and we are able to make a reasonable guess that the underlying trouble is an altered brain metabolism. I have felt for some time that perhaps Goldberger's greatest contribution to medicine eventually may turn out to be not the discovery that pellagra is a dietary deficiency disease, but rather the first recognition of a specific treatment for a major psychosis."

Do other forms of nervous and mental disease have concrete biochemical causes? How can vitamins and other food factors affect thinking processes? If vitamin deficiencies precipitate certain types of mental dysfunction, can vitamin supplements, on the other hand, heighten the intelligence level of normal persons? All of these questions have been answered, at least in part, by combined research in nutrition, neurology and psychiatry within the relatively brief space of about ten years. The role of nutrition in psychiatry, however, constitutes an embryonic field whose great promise lies not in what has already been discovered, but in what achievements are yet to be expected as a result of the basic principles unearthed.

The Biological Action of the Vitamins:

As the science of nutrition advanced from the "dietetic" phase to the point where chemical explanations were sought for the characteristic behavior of the various food nutrients, much of the mystery surrounding the effects of the vitamins was cleared away. The gradual merging of the fields of vitamin chemistry and of enzyme chemistry, for example, brought to light the fact that certain of the vitamins function by virtue of constituting essential, integral portions of enzyme systems. Since all of the life processes are dependent upon the activating forces of enzymes, it is readily understood that any impairment of such enzymes resulting from deficiency of their vitamin components, would lead to a breakdown of the biological machinery. The clinical symptoms and signs of vitamin deficiency, therefore, represent outward evidence of such a breakdown in body metabolism. Whether the symptoms are manifested in the skin, eyes, muscles, nerves, mucous membranes or brain simply depends on what particular vitamin-enzyme system has been thrown out of gear. On the basis of these facts it is quite understandable that vitamin deficiencies may result not only in physical symptoms such as weakness, fatigue, muscle soreness, eye disturbances, burning of the feet, skin eruptions, soreness of the mouth and tongue, enlargement of the heart, and involvement of the nerves,* but even in mental breakdown due to derangement of normal metabolic processes.

Vitamins in Brain Metabolism: The vitamins have been divided roughly into two groups: Those demonstrated to be necessary for prevention of degenerative changes in the central nervous system, and those not required directly for maintenance of nerve structure. The first group includes most of the B vitamins: Thiamine, niacin, riboflavin, pantothenic acid and pyridoxine. The second includes vitamins A, D, C and E (3). The actual structural changes in the nervous system caused by a lack of the members of the first group have been produced and studied experimentally in animals. They have been observed clinically in human patients as well. In most cases, however, the exact metabolic processes underlying these disturbances have not been clarified, except in the case of thiamine deficiency. The second group of vitamins does not act directly on the brain, but may influence brain metabolism by the effects on other parts of the body. For example, lack of vitamin A retards skeletal growth. Meanwhile, however, the central nervous system develops uninterruptedly. The effects of the disproportionate growth of the two systems result in mechanical damage to the nervous system due to

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**cf. Borden's Review of Nutrition Research,* November, 1946—"Experimental Vitamin Deficiency in Man."*

overcrowding (4, 5). Lack of vitamin D increases nervous irritability by lowering the calcium concentration in the blood. Insufficient vitamin C produces minor hemorrhages in the brain, as well as elsewhere throughout the body, because its absence causes increased fragility of the blood capillaries. Wortis *et al* (6) have suggested that, in addition, vitamin C may also play a direct role in nerve tissue metabolism. Vitamin E deficiency causes severe degeneration of skeletal muscle* which in turn has a complex, indirect relationship to the central nervous system.

Carbohydrate Metabolism and Vitamins: In order to understand the influence of the B complex vitamins on brain function, it is necessary to know the mechanisms involved in the metabolism of carbohydrate as it occurs in this organ. The activities of the human brain are supported chiefly by energy derived from the oxidation of carbohydrate, specifically glucose. This fact is supported by experimental and clinical evidence (7, 8, 9) derived from studies under normal conditions and in various states of disordered metabolism such as diabetes.

The oxidation of carbohydrate in the brain differs significantly from its oxidation in other organs. First, the brain oxidizes carbohydrate almost exclusively. Other organs utilize fat as well. Second, the brain does not require insulin for the oxidation of carbohydrate. But muscle, heart, kidney and liver are dependent upon this hormone for the effective utilization of carbohydrate. Finally, more than one path of glucose oxidation is possible in brain metabolism. Any interference with the primary sequence of oxidation does not result in an interruption of the process. Oxidation merely continues by an alternate pathway.

The vitamins are important in brain metabolism because certain ones are integral parts of enzyme systems which are required at the various stages of carbohydrate oxidation. The enzyme *carboxylase* which is required for the decarboxylation of pyruvic acid, a product formed during the intermediate metabolism of glucose, is made up of three essential parts: A protein molecule, the mineral — magnesium, and a "coenzyme," which has been identified as a phosphoric acid salt of the vitamin, thiamine (Fig. 1).

$$\text{Carboxylase} = \begin{cases} \text{protein molecule} & \text{(enzyme base)} \\ \text{magnesium} & \text{(linking molecule)} \\ \text{diphosphothiamine} & \text{(co-enzyme or prosthetic group)} \end{cases}$$

Fig. 1—The chemical make-up of the enzyme, carboxylase

*cf. *Borden's Review of Nutrition Research*, June, 1945 and September, 1945—"Experimental Vitamin E Deficiency" and "Vitamin E in Veterinary and Clinical Medicine."

All of the enzymes are constructed along similar lines: A basic protein molecule and a coenzyme (also known as a prosthetic group because it is an added grouping attached to the main protein) which are linked together through an intermediary compound. Because diphosphothiamine is the coenzyme part of carboxylase, it is known as *cocarboxylase.* Lack of thiamine in the diet, therefore, leads to a decrease in cocarboxylase which the body makes by phosphorylating free thiamine. A decrease in the amount of cocarboxylase, in turn, interferes with the manufacture of the enzyme carboxylase. The absence of this enzyme results in the interruption of glucose oxidation at the stage where pyruvic acid is formed. Without the presence of carboxylase, pyruvic acid accumulates in the blood and leads to abnormal metabolic reactions. It is these reactions which cause some of the outward manifestations attributed to thiamine deficiency.

In a similar manner, riboflavin constitutes the activating prosthetic group of certain other enzymes known as the flavoproteins. Nicotinic acid is known to be a required coenzyme for at least two enzymes. A reduction in the concentration of any of these coenzymes leads to altered metabolism such as has been described in the case of cocarboxylase deficiency.

Pyridoxine, pantothenic acid and biotin are closely associated with proteins in the living cell, but evidence of their possible function as coenzymes is still lacking. Vitamin C, *p*-aminobenzoic acid and vitamin A also are implicated as possible coenzymes, but sufficient data is not yet available to clearly establish their activity in these roles.

Neurological Signs of Vitamin B Deficiency:

Experimental studies have shown that vitamins are essential not only for the uninterrupted functioning of vital metabolic processes, but that they also play a significant part in maintaining the physical integrity of the nerves.

A dietary deficiency of the vitamin B complex in man has been shown to result in numerous degenerative changes in the brain, spinal cord and peripheral nerves — nerves in the extremities. In some cases certain of these lesions can be traced to lack of a single vitamin of the B complex. It has not always been possible, however, to clearly differentiate the effects of the individual members, except by correlation with evidence from animal studies. The following is a brief description of human nervous system lesions resulting from a general B complex deficiency (14).*

*The extensive literature on the histopathology of the nervous system in the B-avitaminoses is beyond the scope of this *Review.* Those who are interested in this phase of vitamin deficiency are referred to the detailed reviews by Zimmerman (14, 15, 16).

The Peripheral Nerves: Microscopic examination of these nerves reveals actual degenerative alterations in their structure. Earliest of these is the gradual, progressive disappearance of the outer protective nerve covering, *the myelin sheath.* The layer of cushioning fat within this disintegrating sheath becomes exposed and ultimately the nerve axon itself undergoes destructive alterations. The different nerves vary in the degree of involvement, those of the lower extremities usually suffering first and more extensively.

The Spinal Cord: The spinal cord is not as uniformly affected in vitamin B deficiency as are the peripheral nerves. When it is, only certain portions are involved. The changes are similar to those in the peripheral nerves, involving progressive demyelinating lesions in specific tracts within the spinal cord.

The Brain: The chief symptoms of B deficiency as evidenced by examination of brain tissue consist of numerous tiny hemorrhages in certain preferential areas of the brain. These are caused by swelling and congestion of the blood capillaries and are often accompanied by profound cellular changes in the blood and by thickening of the capillaries. All of this results in considerable obstruction and interference with normal blood circulation, causing a type of local anemia of the brain.

Correlation of Metabolic and Nerve Changes with Mental Symptoms:

From the existing evidence it is apparent that vitamins exert a two-fold effect on nervous and mental activity. First, a deficiency of certain vitamins may result in actual degenerative changes in the structure of the brain and of the nerves. Second, an insufficiency of vitamins which constitute essential portions of enzyme systems leads to disruption of normal brain metabolism. Impairment of brain and nervous system action in either of these two ways is manifested by impaired neurologic responses throughout the body and by derangement of intellectual and emotional faculties.

Although the structural changes in the nervous system resulting from vitamin B complex deficiency have been studied in considerable detail, both in human subjects and experimentally, the actual metabolic disturbances involved in these deficiencies have not been entirely clarified, except, as has already been indicated, in the case of thiamine deficiency.

Thiamine Deficiency Changes (In Animals): Lack of vitamin B_1 produces pathological changes in nerve structure as well as biochemical disturbances in the central nervous system. The latter include an abnormally increased concentration of pyruvic acid, a diminished oxygen consumption

and a lowered respiratory quotient. In addition, actual neurological changes have been observed in those parts of the body which are controlled by the affected portions of the brain. In pigeons, for example, the experimental studies have shown that biochemical changes occur in the optic lobes of the brain (10). This portion of the brain controls the motor activities of the bird. Vitamin B_1-deficient pigeons exhibit characteristic convulsions and spasms. In the light of the information just described, this may be traced to the metabolic dysfunction of the optic lobes. Similar reactions in thiamine-deficient rats were traced to a depression of the brain metabolism in an area containing motor nuclei (11).

The outward nervous manifestations of thiamine deficiency in experimental animals vary both with the species and with the extent of the dietary inadequacy. In severe thiamine deficiency there is a sudden onset of weakness. This often extends into collapse and is accompanied by severe muscular spasms. The reaction is very rapid in the dog and unless treated, is fatal within two or three months. Pigeons and chicks, on the other hand, develop the symptoms more slowly and with less severity.

Examination of the tissues reveals demyelinating changes of the peripheral nerves identical with those seen in man. Animals suffering from mild, prolonged thiamine deficiency comparable to human subclinical states, may live for as long as a year. They develop a chronic, progressive spasticity of the hind legs; certain reflexes are lost; unsteadiness, staggering and vomiting develop. Thiamine administered early in the disease effects a prompt cure. If delayed until the terminal stages of the disease are reached, thiamine therapy is powerless to permit repair of the severe nerve damage. Thiamine deficiency has also been observed to produce hemorrhagic involvement of the brain in the pigeon, rat, dog and fox identical in all respects with the human disease known as Wernicke's syndrome, thus indicating the thiamine-deficiency nature of this nervous disorder.

Thiamine Deficiency Changes (In Man): The symptoms accompanying disturbances of brain function in humans have been subjected to finer analyses than have the symptoms of any other species. Studies of thiamine deficiency in man, therefore, have permitted excellent correlation between the biochemical changes and the neurological and mental symptoms. Although all parts of the central nervous system may be involved as a result of dietary inadequacy of vitamin B_1, the changes are not equally severe throughout the system. In some cases the peripheral nerves may become involved. In others, portions of the spinal cord may be affected. In still others, certain parts of the brain itself present symptomatic changes.

In any case, pyruvic acid accumulates in the affected part and pours out into the blood stream. Blood tests on patients suffering from the disorder known as peripheral neuritis — a result of thiamine deficiency due to alcoholism — have actually revealed abnormally high levels of pyruvic acid in 45 out of 48 subjects in one study (12). The symptoms presented in this disease vary with the neurological origin of the pyruvic acid. Thus, involvement of certain specific nerve areas has been shown (13) to result uniformly in paralysis of the eye muscles, clouding of consciousness and inability to perform coordinated muscular activities (Wernicke's syndrome).

Following the lead offered by comparative animal studies, Wortis *et al* (13) administered thiamine in these cases. Normal function of the eye muscles was restored in from one to three days, the pyruvic acid level in the blood dropped to normal and the mental status improved. No effect, however, was noted on the general muscular incoordination. These results confirmed the casual relationship of vitamin B_1 deficiency to the development of a major part of Wernicke's syndrome in alcoholics.

Himwich *et al* (17) in a study of the carbohydrate metabolism of the brain during the deficiency of various members of the vitamin B complex, were able to demonstrate some correlation between the biochemical changes induced by thiamine deficiency and the characteristic mental derangement of pellagra. By comparative determinations of the oxygen content of the blood entering and leaving the brain of their patients, they were able to demonstrate a marked depression of brain metabolism traceable to an interference with the oxidation of pyruvic acid. Administration of cocarboxylase, the thiamine-containing enzyme required for the oxidation of pyruvic acid, led after one week to an increase in the brain metabolism and improvement of mental state in one patient. The other patients, however, examined only three hours after therapy, showed no signs of improvement.

In man as in animals, the symptoms of mild chronic thiamine deficiency differ from those observed in the severe, acute form. Early mental and nervous indications of thiamine deficiency include general weakness, lassitude, nervousness, apprehension, irritability, suspicion, forgetfulness, insomnia, hypersensitivity to pain — particularly in the extremities — loss of appetite, headaches, burning of the stomach and of the feet and similar symptoms.* In severe thiamine deficiency there may develop the clinical disorders known as anorexia nervosa, peripheral neuritis, Wernicke's syndrome, neurasthenia, multiple neuritis, possibly the Korsakoff syndrome, and others.†

**cf. *Borden's Review of Nutrition Research,* November, 1946—"Experimental Vitamin Deficiency in Man."*

†The clinical aspects of mental and neurologic disorders induced by vitamin deficiency will be discussed in the January, 1947 issue of *Borden's Review of Nutrition Research.*

Nicotinic Acid: Most of the mental symptoms observed in pellagrins have been found to respond to thiamine therapy. In certain instances, however, pellagrins without obvious signs of thiamine deficiency have also displayed symptoms of mental derangement. It has been found that, in these latter cases, improved mental response may be obtained with nicotinic acid (17). Unlike the observations in thiamine deficiency, however, it has not been possible to demonstrate a marked decrease in brain metabolism in nicotinic acid deficient patients. While the normal difference in value between arterial and venous oxygen levels is set at 6.7 volumes per cent, this value dropped only slightly to 6.2 in pellagrins without thiamine deficiency, as compared to a drop to 4.7 in patients lacking sufficient thiamine. Despite the lack of corroborative evidence, however, the nature of the degenerative changes resulting from nicotinic acid deficiency strongly suggest a depression of the energy supplies of the brain.

In instances where the deficiency of nicotinic acid is acute and very severe, however, it is thought that a depression of the brain metabolism does actually occur. As an example, Jolliffe and associates (18) have observed a special type of brain degeneration, heretofore almost always fatal, which they attribute to the rapid development of a complete nicotinic acid deficiency. They were able to secure positive therapeutic effects, apparently based on a stimulation of the rate of brain metabolism, through the administration of nicotinic acid. Additional indication that nicotinic acid may result in actual physical changes in the nervous system is to be found in the work of Zimmerman *et al* (19) who observed spinal cord lesions of moderate degree in nicotinic acid deficient dogs.

Prior to the work of Jolliffe *et al* (18), Cleckley, Sydenstricker and Geeslin (20) had reported on the successful treatment of a group of stuporous patients who showed a dramatic response to nicotinic acid therapy. They concluded that the progressive loss of special sense faculties leading to profound stupor may be the only sign of acute, severe pellagra developing, like the brain encephalopathy reported by Jolliffe, so rapidly that it precedes the development of the typical skin lesions characteristic of pellagra. Subsequent studies by these workers confirmed these theories (21).

Of interest in these cases is the unusually large dosage of nicotinic acid required as compared with the dosage for conventional, typical forms of pellagra. The mechanism of the action of nicotinic acid in these cases is in some doubt. It would seem that these patients differ from the usual cases of pellagra. It has been suggested that the nicotinic acid may exert a simple pharmacological effect through its vasodilator properties which stimulate

the flow of blood in the brain (22). However, the pharmacological theory must remain doubtful since nicotinic acid amide does not have the vasodilating effects of the acid, but nevertheless, relieves the nervous manifestations. In general, it is believed that the action of the vitamin is more fundamental than a simple, temporary increase in blood flow through the brain, and is therefore related to a true metabolic disturbance arising from a dietary insufficiency of the vitamin.

Other B Complex Vitamins: Riboflavin deficiency has not been clearly linked to mental or neurological disorders in man, but some evidence exists that it has a significant role in maintaining the integrity of the nervous system in experimental animals. In severe, acute riboflavin deficiency dogs develop symptoms of profound collapse in from 100 to 150 days. They can be cured by prompt administration of riboflavin. No actual neurologic lesions are apparent (3). In chronic, mild riboflavin deficiency, however, degenerative changes in the nerves and in the spinal cord are observed. They increase in severity with the length of time on the deficient diet (23, 24). The changes consist of degeneration of the protective myelin sheath of the nerves similar to that seen in thiamine deficiency, but require about twice the time before they become apparent. Similar lesions have been observed in pigs, chicks and rats.

Pyridoxine (vitamin B_6) deficiency has been shown to result in epileptic-like attacks in pigs and dogs in the acute stages, and in congestive heart failure in the chronic stages. Aside from the convulsive attacks, however, neurological manifestations are not prominent, although anatomic evidence of demyelination of peripheral nerves and of the spinal cord has been reported. Again, like the changes of riboflavin deficiency these lesions are indistinguishable from those of thiamine deficiency except in degree. In man, pyridoxine has been implicated to a limited extent in the neurological disease of Parkinsonism, some success in treatment having been reported by Jolliffe (25, 26), Spies *et al* (27), and others (28, 29, 30). The mechanisms underlying its action are not at all clearly understood, nor is the response of the disease to pyridoxine always favorable. Nevertheless, in view of the scattered reports of improvement obtained with pyridoxine especially in the early stages of the disease, it is considered advisable to give it a trial in these otherwise hopeless cases.

Pantothenic acid has been shown to be essential in the preservation of the spinal cord of chicks, (31) but no evidence has yet been obtained to relate this vitamin to the health of the nervous system of other animals or of man.

Conclusion:

From the experimental evidence so far at hand, several significant facts have emerged with respect to vitamin intake and its influence upon mental and neurological health. It has been demonstrated that dietary insufficiency of certain vitamins may lead to profound degenerative changes in the central nervous system and to abnormal biochemical influences as a result of disordered metabolism. That these physical and chemical pathologies result directly in interference with brain metabolism and consequently with brain function cannot but fail to be apparent. From this, it is easy to correlate the development not only of neurological disturbances, but mental disorders as well, with inadequacy of vitamin intake. Although the exact metabolic disturbances underlying these effects are known in only a few limited instances as yet, there is every indication that current and future research along these lines will yield still more fruitful and promising results.

The following issue of *Borden's Review of Nutrition Research* will discuss in detail the clinical studies of neurologic and psychiatric disturbances associated with vitamin deficiencies.

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NEWS DIGEST

EGG AND MILK CONVALESCENCE—Experience with starving prisoners of war, with wounded and special patients from prison camps and with victims of concentration camps has demonstrated that restoration to normal health in starvation can be accomplished in about one-third the average time by the use of a food mixture containing powdered egg and powdered milk. Of 92,000 soldiers liberated from German prison camps treated with this bland diet, only 8 died, although 40 per cent were suffering from severe starvation and at least 80 per cent were generally malnourished. One week after the introduction of the egg and milk mixture to the Standard Army ration, the sick call rate at Recovered Allied Military Prisoners camps dropped from over 20 per cent to 4 per cent. The mixture is said to taste somewhat like an egg nog or ice cream. Its advantages lie in its concentrated nutritional value and palatability. The mixture is a rich source of superior quality protein which is a prime essential in convalescence. It also provides liberal amounts of fat and carbohydrate for energy purposes. *Science New Letter,* Oct. 19, 1946.

THIAMINE IN CHEESE—The fate of thiamine in the manufacture of cheddar cheese and the effect of ripening periods has been studied at four two-month intervals covering spring, summer and fall seasons. Both raw and pasteurized milk were used in two different methods of making the cheese. Little or no loss of thiamine was found in either process. A progressive decrease in thiamine content, however, was observed with increased ripening periods. The average retention of thiamine in the cheese was 8.8 per cent. *J. Nutr. 32,* 227 (1946).

CASEIN HYDROLYSATE–Because the nutrition of a premature infant is a complicated problem and since theoretically proteins are of the utmost importance for the nutrition of the premature infant, the following feeding plan was devised. A mixture of amino acids, an enzymatic casein hydrolysate, was fed as a supplement to breast milk to more than 100 premature infants. The daily dose was 2.5 grams of amino acids per kilo of body weight, together with an equal amount of glucose. The infants tolerated the amino acid mixture well, and there were no signs of digestive disturbance. In every instance the feeding of this mixture produced a distinctly higher gain in weight than breast milk alone. A comparison between the effects of this mixture and of a mixture containing undigested casein, glucose, and salts in the same strengths and proportions showed that the gain in weight was consistently greater during the periods when the infants were receiving amino acids than when casein was being administered. By special tests, it was demonstrated that the gain in weight was due to the amino acids. *Lancet 2,* 228 (1946).

VITAMIN A—The development of a water-soluble vitamin A, recently announced, makes available a more readily utilizable form of this vitamin for therapeutic purposes. In children who had previously shown poor absorption of vitamin A in oil, utilization of the water solution of the vitamin was said to be very effective. Experiments with both oil and water solutions of vitamin A indicated an eightfold increase in the blood level of vitamin A when the aqueous solution was administered as compared to the level obtained with oil solutions of the vitamin. *Amer. Chem. Soc. Conv.,* Chicago, Sept. 1946.